



Hemodynamic clinical phenotyping in septic shock

Anousone Daulasim, Antoine Vieillard-Baron and Guillaume Geri

Purpose of review

Recent studies have failed to show significant benefit from a uniform strategy, suggesting that hemodynamic management must be individually adapted in septic shock depending on different phenotypes. Different approaches that may be used to this end will be discussed.

Recent findings

Fluid management is a cornerstone of resuscitation, as the positive fluid balance has been associated with higher mortality and right ventricular failure. Myocardial evaluation is mandatory, as sepsis patients may present with a hyperkinetic state, left ventricular (systolic and diastolic) and/or right ventricular dysfunction, the latter being associated with higher mortality. Statistical approaches with the identification of hemodynamic clusters based on echocardiographic and clinical parameters might be integrated into daily practice to develop precision medicine. Such approaches may also predict the progression of septic shock.

Summary

Different hemodynamic phenotypes can occur at any stage of sepsis and be associated with one another. The clinician must regularly assess dynamic changes in phenotypes in septic shock patients. Statistical approaches based on machine learning need to be validated by prospective studies.

Keywords

clusters, echocardiography, hemodynamics, phenotyping, septic shock

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, with septic shock as the most critical stage of circulatory and cellular metabolism abnormalities [1]. In 2017, an estimated 48.9 million incident cases of sepsis were recorded worldwide leading to 11 million deaths. Although mortality decreased by 53% from 1990 to 2017, sepsis remains one of the highest burdens in public health [2].

Infection triggers a complex host response with both anti-inflammatory and proinflammatory responses, endothelial dysfunction, vasodilation and increased capillary permeability, ultimately leading to organ failure and death. As such, in addition to urgent antimicrobial therapy, adequate initial resuscitation is also needed. An early goal-directed therapy was proposed in 2004 in the first Surviving Sepsis Campaign based on a study by Rivers *et al.* [3], but further studies failed to show significant benefit from this strategy [4,5]. Such a strategy was similar in all septic patients, while it is obvious there are several subgroups of patients who could benefit from different adjustments of treatment. Accordingly, this raises the question of how to identify different

hemodynamic phenotypes of septic shock so as to adjust for specific management trending to individualized medicine.

In the present review, we describe the different ways to delineate such different hemodynamic phenotypes using clinical tools as well as more complex statistical methods.

USUAL BEDSIDE APPROACH

The main clinical feature of septic shock is persistent hypotension [mean arterial pressure (MAP) < 65 mmHg], despite initial fluid resuscitation, which leads to the administration of vasopressors, which are associated with hyperlactatemia [1,6]. Hemodynamic assessment is a crucial step of

Medical Intensive Care Unit, Ambroise Paré Hospital, AP-HP, Boulogne-Billancourt, INSERM UMR 1018, Clinical Epidemiology Team, CESP, Paris-Saclay University, Villejuif, France

Correspondence to Guillaume Geri, Service de Médecine Intensive Réanimation, Hôpital Ambroise Paré, 9 avenue Charles de Gaulle, 92100 Boulogne Billancourt, France. Tel: +33 1 711 677 33; e-mail: guillaume.geri@aphp.fr

Curr Opin Crit Care 2021, 27:290–297

DOI:10.1097/MCC.0000000000000834



SHOUT
SHARE IT

KEY POINTS

- Different hemodynamic phenotypes may occur in septic shock which can be associated with one another.
- Combination of clinical, biological and hemodynamic parameters is the best approach to better determine these clusters.
- From this point of view, echocardiography gives accurate information.
- Statistical approaches based on machine learning need to be validated at the bedside.

resuscitation as it guides initial therapy during the first hours of healthcare.

The classical clinical phenotyping approach is based on the evaluation of volemia, vasoplegia and myocardial dysfunction [both left ventricular (LV) and right ventricular (RV)]. In the past, Hess *et al.* [7] reported hemodynamic alterations as a succession of different states: the first one very soon after admission, with a low flow state due to hypovolemia; the second after initial fluid resuscitation, reflecting the classical 'warm shock', with a hyperdynamic state and high cardiac output due to vasoplegia; and the last state very late, with cardiac failure and multiple organ failure finally leading to death; however, such a description is challenged by the fact that septic shock does not follow a linear natural history of clearly defined phenotypes succeeding one another. On the first day of treatment of septic shock, hemodynamic evaluation by echocardiography suggests that all phenotypes may occur, separately or combined [8].

Vasoplegia and hypovolemia

Systemic vasodilation and increased vascular permeability in septic shock lead to a state of hypovolemia (both absolute and relative) due to decreased stressed volume. Therefore, one of the main components of initial resuscitation is fluid management to restore intravascular volume, increase cardiac output and lessen organ dysfunction. However, aggressive fluid administration may lead to excessive capillary leak and pulmonary edema. Aggressive fluid resuscitation may also promote RV failure [9]. Vasopressor infusion is another way to restore the stressed volume, thus increasing systemic venous return and finally correcting relative hypovolemia. Fluid overload is associated with increased mortality in critically ill patients [10^{***}]. The clinician must constantly assess fluid responsiveness to avoid this pitfall.

Assessing volemia and fluid responsiveness is one of the most difficult tasks in clinical practice and is covered in another article in this issue of the journal. Briefly, echocardiography may be of great help, as invasive static parameters fail to accurately predict the need for and response to fluids [11,12]. Among all the echocardiographic parameters, respiratory variation of the superior vena cava (SVC) in mechanically ventilated patients is the most accurate parameter, providing a grey zone approach is applied [13] (Fig. 1). End-expiratory diameter of the inferior vena cava (IVC) can be used to determine the response (small IVC) or the absence of response (dilated IVC) in only 30% of cases [14] (Fig. 1); however, fluid responsiveness is far from being systematically assessed in routine practice. The FENICE study in 2015 showed that only 36% of patients were evaluated with static markers of preload and 22% with dynamic indices of preload responsiveness [15]. More than 40% of them were not evaluated at all [15].

Left and right ventricular evaluation

Hyperkinetic state (also known as 'warm shock') has been described since the 1980s and was defined as an early stage of septic shock characterized by decreased peripheral vascular resistance (i.e., LV afterload) and increased catecholamine production inducing increased LV systolic function [16]. Despite the seemingly preserved/enhanced cardiac function, peripheral tissue still suffers from hypoperfusion due to microcirculation abnormalities [17]. The spectrum of the hyperkinetic (or hyperdynamic) state encompasses hypovolemic patients with low cardiac output (favoring left intraventricular obstruction and high mortality, 18), severe septic shock patients with a dramatic fall in arterial resistance, and sometimes well-resuscitated patients too. As such, the prognosis of patients in the hyperkinetic state is extremely heterogeneous [18–20].

Conversely, more than half of patients presenting with septic shock may develop LV systolic dysfunction with low LVEF and cardiac output [21,22] at any stage of the disease. Multiple factors are being identified, all can lead to intrinsic myocardial depression [23]. The association between LV systolic dysfunction and mortality is mixed. Meta-analysis failed to show an association between LVEF and mortality [24,25], suggesting that echocardiographic measures must be interpreted in a comprehensive evaluation of the patient with the goal of assessing matching between cardiac function and oxygen demand.

In contrast, LV diastolic dysfunction has also been described and is associated more consistently

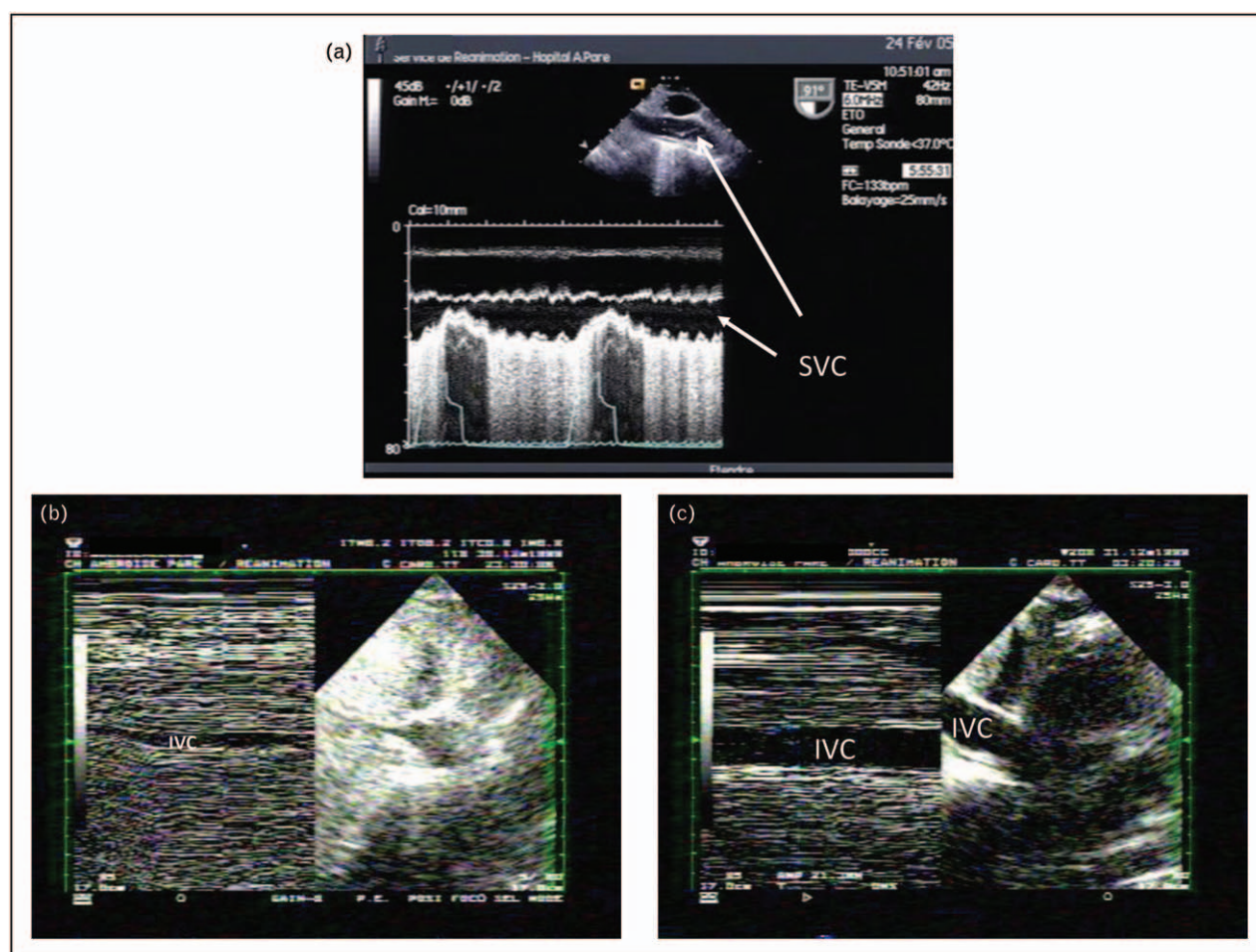


FIGURE 1. Echocardiographic parameters to guide fluid resuscitation. (a) Upper esophageal view by transesophageal echocardiography combining 2D with time motion study in a mechanically ventilated patient with septic shock. Superior vena cava (SVC) respiratory variations suggested that the patient was still hypovolemic. (b) Subcostal view (2D and time-motion study) in a fluid responsive patient. The inferior vena cava (IVC) was very small. (c) Subcostal view (2D and time-motion study) in a nonfluid responsive patient as suggested by a significantly dilated IVC.

with poor outcomes [26,27]. RV dysfunction has been described by Kimchi *et al.* [28] and was found independently of the LV dysfunction. When defined as a decreased RV fractional area change (RVFAC < 35%) or tricuspid annulus systolic planar excursion (TAPSE < 1.6 cm), RV systolic dysfunction occurs in up to half of septic shock patients [29^{***}]. It has been associated with both worse short-term [30^{*}] and long-term prognosis [31]. RV failure was recently proposed to be the association of a dilated right ventricle, seen using echocardiography, with an elevated central venous pressure (CVP) reflecting systemic congestion [32,33] (Fig. 2). Applying this definition in a population of 282 patients with septic shock, all mechanically ventilated, we reported an incidence of RV failure of around 40% [34^{***}].

Echocardiography is then a crucial tool in the evaluation of patients with septic shock and has a

real impact on resuscitation. In addition to its clinical impact in the daily management of septic shock patients, echocardiography allows the clinician to cluster septic shock patients leading to individualized therapy.

CLUSTERING AND MACHINE LEARNING: THE NEAR FUTURE?

In the last few years, computers have become increasingly powerful and as such, calculation speed and power have also skyrocketed, allowing physicians and researchers to delve into more complex models. Clustering, also known as unsupervised classification, is designed to determine classes (or clusters) of patients based on other data, without any prior hypothesis on the number or nature of the clusters. This mathematical method has been recently applied in the intensive care unit to

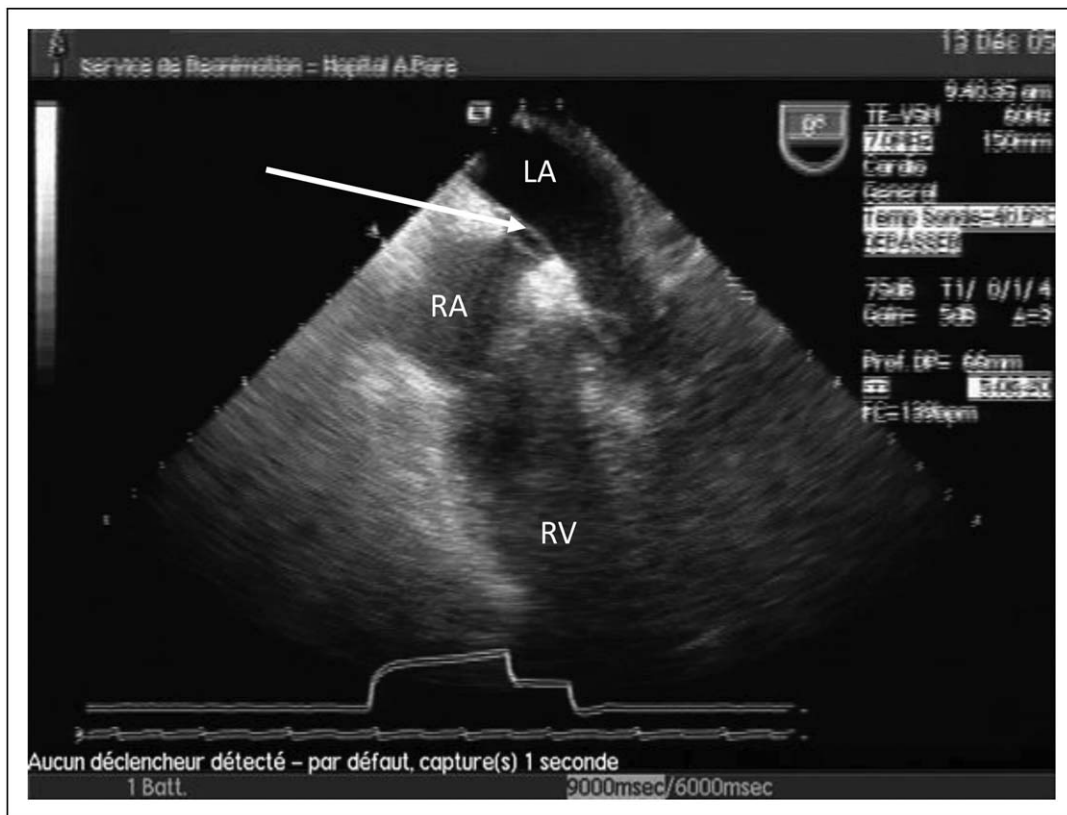


FIGURE 2. RV failure in a patient ventilated for septic shock. The mid-esophageal view by transesophageal echocardiography demonstrated major dilatation of the right ventricle and the right atrium. The bulging of the interatrial septum toward the left atrium reflects high pressure in the right chambers and systemic congestion. RV, right ventricular.

enhance our comprehension of hemodynamic alteration and to predict disease progression and even outcome.

Hemodynamic profile and management

The main potential advantage of the clustering approach compared to the 'classical' one discussed above is that hemodynamic variables recorded by echocardiography or any other hemodynamic monitoring device may be automatically integrated with clinical parameters and patient characteristics to give a more precise cardiovascular phenotype, the computer doing with more precision and accuracy what frontline physicians are doing in their mind at the bedside. This could allow precision medicine rather than the application of the same management to every patient [35–37]. A good illustration that the 'one size fits all' approach does not work is given by a recent randomized controlled trial about the impact of levosimendan in septic shock. The only inclusion criterion was the need for vasopressors for more than 4 h [38]. Unsurprisingly, the study was negative, but the authors were lucky

not to observe any deleterious effect in the levosimendan group.

We recently proposed such a statistical approach gathering clinical, laboratory, and echocardiographic data, to focus on cardiovascular clusters (phenotypes) in septic shock [39]. We used variables that are all routinely available: sepsis-related organ failure assessment (SOFA) score, simplified acute physiology score II (SAPS II), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), central venous pressure (CVP), central venous oxygen saturation (ScvO₂), volume of initial fluid resuscitation, use of catecholamine, serum lactate and arterial blood gases. Hierarchical clustering on principal components sequentially uses agglomerative hierarchical clustering and *k*-means clustering to improve partition [40,41]. For each identified cluster, the three most important variables were identified and their diagnostic performance was evaluated by both area under the ROC curve of a multivariable logistic regression and sensitivity, specificity, and negative and positive predictive values depending on thresholds.

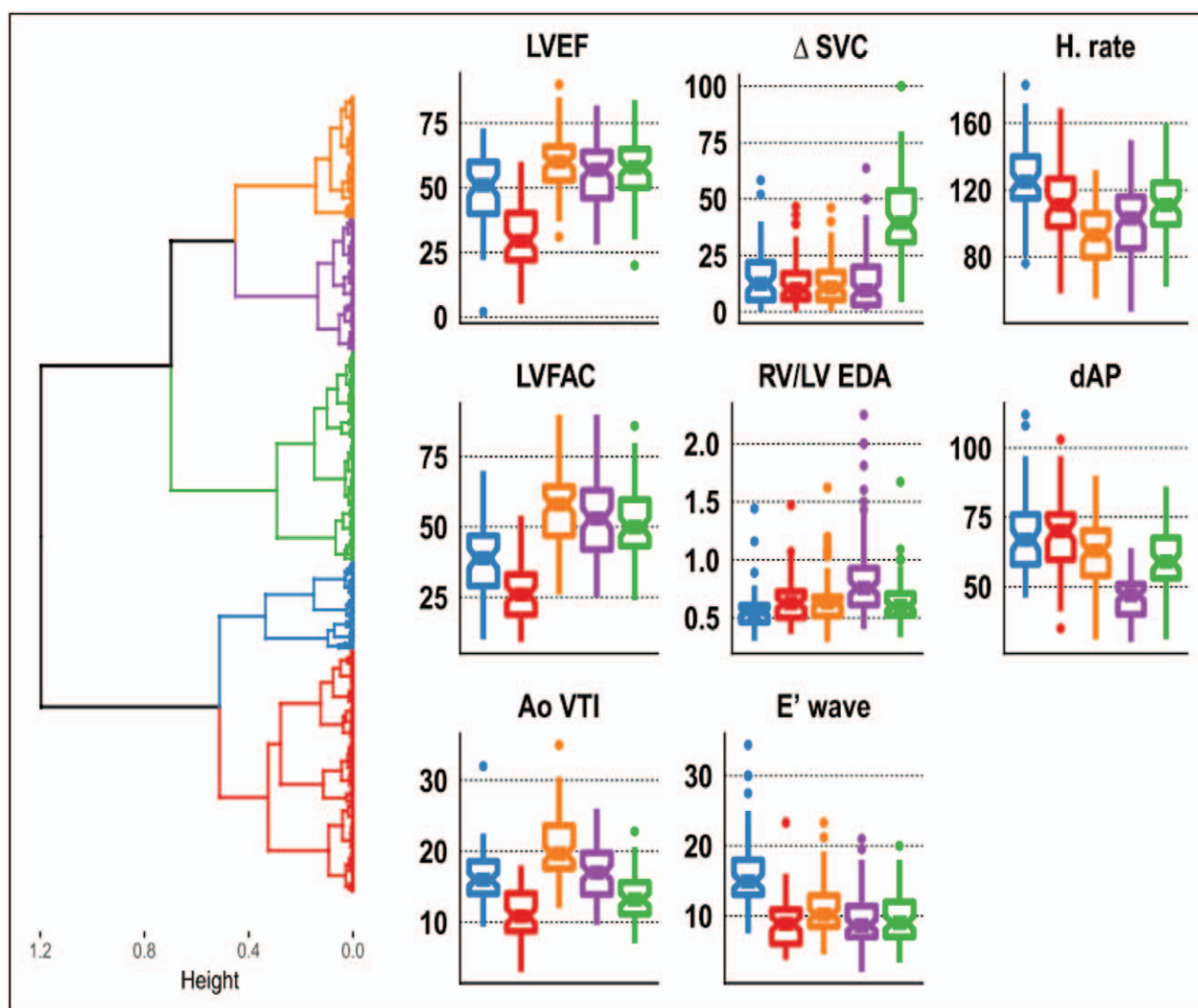


FIGURE 3. Hierarchical clustering dendrogram and boxplots of main variables, identifying five distinct clusters: 'well resuscitated' phenotype in blue, 'LV systolic dysfunction' in red, 'hyperkinesia' in orange, 'RV failure' in purple and 'hypovolemic' in green. From reference [39] with permission. LV, left ventricular; RV, right ventricular.

The first phenotype reported in 360 patients was the 'well resuscitated' patient presenting neither LV/RV dysfunction nor fluid responsiveness. This was reported in 16.9% of cases. The second phenotype, observed in 17.7% of cases, defined LV systolic dysfunction with abnormal echocardiographic parameters of LV systolic function and decreased aortic velocity time integral (VTI); the mortality rate was increased. The third phenotype represented a hyperkinetic state with normal or supranormal LV systolic function with an elevated aortic VTI and with no sign of fluid responsiveness; heart rate was unexpectedly not significantly increased. The fourth phenotype potentially concerned RV failure in which the right ventricle was dilated and blood pressure was decreased. Finally, the last phenotype reflected a 'still hypovolemic' state with fluid responsiveness (Fig. 3 with permission, Table 1).

Whether this approach is able to provide crucial information about the evolution of the hemodynamic profile during the ICU stay should be clarified in the future, as this pilot study only evaluated phenotypes in a snapshot manner.

From differentiating clusters to individually predicting progression to septic shock

The first hours of resuscitation after a septic shock diagnosis are critical. In patients with sepsis, the response to initial resuscitation guided by the characterization of different cardiovascular phenotypes may predict the risk of progression to septic shock. Liu *et al.* [42] used machine learning to generate a risk score based on serum lactate level, cardiovascular SOFA score, heart rate, partial pressure of oxygen, a fraction of inspired oxygen and decreased Glasgow

Table 1. Cardiovascular cluster definitions and classification performances, data from reference [39]

Cardiovascular clusters	Definition	Statistical performances
LV systolic dysfunction	LVEF < 40%, LVFAC < 33%, aortic VTI < 14 cm	Se 53.7%, Sp 97.6, PPV 83.3%, NPV 90.9%
Hyperkinesia	Aortic VTI > 20 cm, LVFAC > 58%, heart rate < 106 bpm	Se 17.9%, Sp 98.2%, PPV 75%, NPV 79.7%
RV failure	RV/LV EDA > 0.8, SAP < 100 mmHg, DAP < 51 mmHg	Se 29.6%, Sp 98.9%, PPV 88.9%, NPV 82.9%
Hypovolemic	Aortic VTI < 16 cm, E wave < 67 cm/s, Δ SVC > 39%	Se 25.7%, Sp 99.3%, PPV 90%, NPV 84.7%

Δ SVC, respiratory variations of the superior vena cava; DAP, diastolic arterial pressure; LV, left ventricle; LVEF, left ventricular ejection fraction; LVFAC, left ventricular fractional area change; NPV, negative predictive value; PPV, positive predictive value; RV, right ventricle; SAP, systolic arterial pressure; Se, sensitivity; Sp, specificity; VTI, velocity–time integral.

Coma Score. The risk score was updated each time a new patient feature was measured. Using a certain threshold, three states were defined: sepsis, a ‘pre-shock’ state and septic shock, and these were well correlated with clinical progression [42] (Fig. 4 with permission). The use of this risk score allowed earlier recognition of the seriousness of a patient’s condition, well before patients meet the Sepsis-3 definition of shock.

Prognosis of sepsis and septic shock in the ICU

Knox *et al.* [43] identified four distinct clusters of multiple organ dysfunction syndrome (MODS) in severe sepsis and septic shock based on a neural network that analyzed clinical and laboratory data:

shock with renal dysfunction, minimal MODS, shock with hypoxemia and altered mental status, and hepatic dysfunction. This classification went beyond the classical definition of septic shock, as a septic shock was associated with the first and third clusters, but the highest mortality was observed within the fourth, regardless of the cause of sepsis. These results were confirmed later by Seymour *et al.* [44].

Sub-categories of septic shock: what’s next?

The next step of modeling needs to answer daily routine questions: will my medical intervention change the course of my patient’s disease? Are these new clinical and/or laboratory data predictive of a favorable or unfavorable outcome? In statistics, this

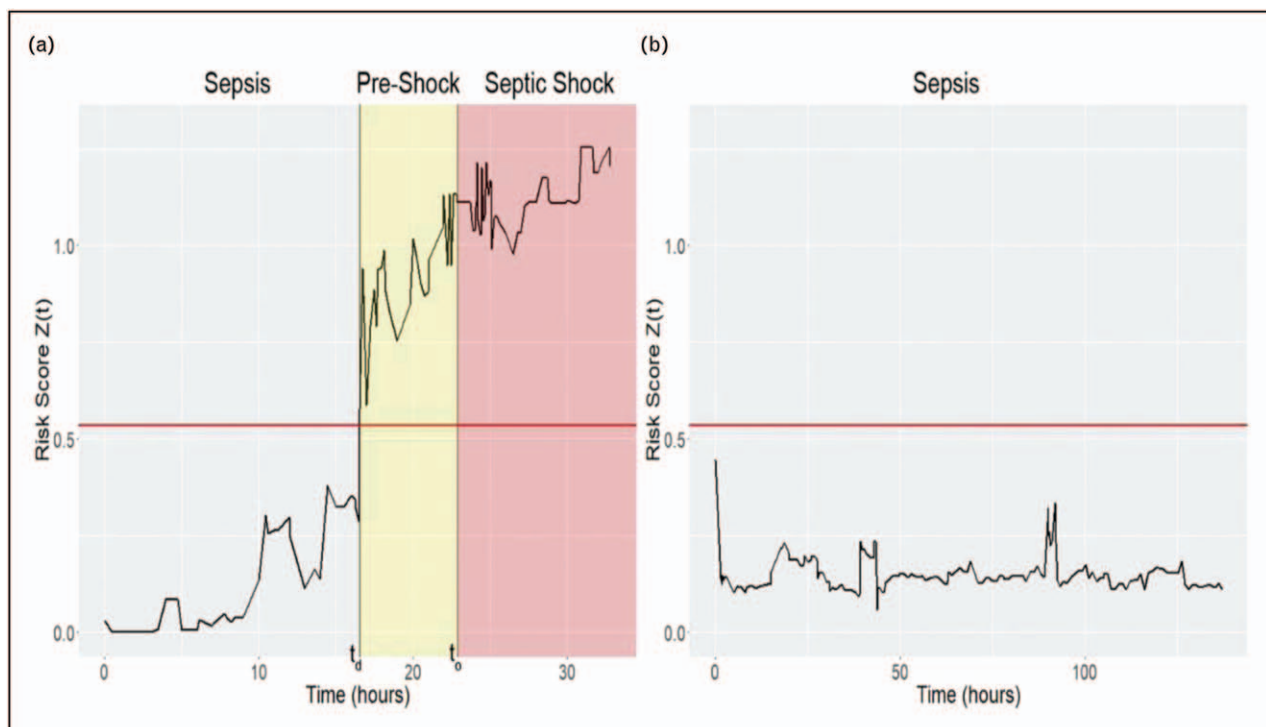


FIGURE 4. Risk score trajectories in a patient who developed (a) and did not develop (b) septic shock. The detection threshold is indicated by the red line. From reference [42] with permission.

approach is called Bayesian inference, which is the use of the latest information to update the probability of a hypothesis. Dynamic models must be identified and validated in order to be of use in the ICU.

Nowadays, these modern tools still need to be investigated and approved with the help of controlled randomized studies before becoming routinely available. Statistical approaches to sepsis and septic shock might soon become one step closer to fully personalized medicine, from identifying septic phenotypes to predicting treatment response, progression to septic shock, and its prognosis.

CONCLUSION

Different hemodynamic phenotypes can occur at any stage of septic shock and be associated with one another. The clinician must regularly assess dynamic changes in phenotypes using a combination of clinical, biological and echocardiographic parameters. Statistical approaches based on machine learning need to be validated by prospective studies.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

A.D. and G.G. did not declare any conflict of interest; A.V.B. received a grant from GSK company for clinical research.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Singer M, Deutschman CS, Seymour CW, *et al.* The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; 315:801–810.
2. Rudd KE, Johnson SC, Agesa KM, *et al.* Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* 2020; 395:200–211.
3. Rivers E, Nguyen B, Havstad S, *et al.* Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Eng J Med* 2001; 345:1368–1377.
4. Peake SL, Delaney A, Bailey M, *et al.* Goal-directed resuscitation for patients with early septic shock. *N Eng J Med* 2014; 371:1496–1506.
5. Yealy DM, Kellum JA, Huang DT, *et al.* A randomized trial of protocol-based care for early septic shock. *N Eng J Med* 2014; 370:1683–1693.
6. Seymour CW, Liu VX, Iwashyna TJ, *et al.* Assessment of clinical criteria for sepsis for the third international consensus definitions for sepsis and septic shock. *JAMA* 2016; 315:762–774.
7. Hess ML, Hastillo A, Greenfield LJ. Spectrum of cardiovascular function during gram-negative sepsis. *Prog Cardiovasc Dis* 1981; 23:279–298.
8. Vieillard-Baron A, Prin S, Chergui K, *et al.* Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. *Am J Respir Crit Care Med* 2003; 168:1270–1276.
9. Greyson CR. Pathophysiology of right ventricular failure. *Crit Care Med* 2008; 36(Suppl):S57–S65.
10. Messmer AS, Zingg C, Müller M, *et al.* Fluid overload and mortality in adult critical care patients – a systematic review and meta-analysis of observational studies. *Crit Care Med* 2020; 48:1862–1870.
- A meta-analysis including 31 076 patients (31 observational & 3 randomized controlled trials) found an adjusted risk of mortality per liter increase of cumulative fluid balance of 1.19 in general ICU patients. Higher mortality was also observed in subgroups (surgery, sepsis, respiratory failure).
11. Bentzer P, Griesdale DE, Boyd J, *et al.* Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA* 2016; 316:1298–1309.
12. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. *Ann Intensive Care* 2016; 6:111. doi: 10.1186/s13613-016-0216-7.
13. Bégot E, Repessé X, Prat G, *et al.* Evaluation comparative des indices échocardiographiques de précharge-dépendance chez les patients en défaillance circulatoire: étude prospective multicentrique HEMOPRED. *Anesth Réanim* 2015; 1(Suppl):A139–A140.
14. Vieillard-Baron A, Evrard B, Repessé X, *et al.* Limited value of end-expiratory inferior vena cava diameter to predict fluid responsiveness, impact of intra-abdominal pressure. *Intensive Care Med* 2018; 44:197–203.
15. Cecconi M, Hofer C, Teboul JL, *et al.* Fluid challenges in intensive care: the FENICE study. *Intensive Care Med* 2015; 41:1529–1537.
16. Schumacher W. Pathophysiology and treatment of septic shock. *Am J Emerg Med* 1984; 2:74–77.
17. Edul VSK, Ince C, Vazquez AR, *et al.* Similar microcirculatory alteration in patients with normodynamic and hyperdynamic septic shock. *Ann Am Thorac Soc* 2016; 13:240–247.
18. Chauvet JL, El-Dash S, Delastre O, *et al.* Early dynamic left ventricular obstruction is associated with hypovolemia and high mortality in septic shock patients. *Crit Care* 2015; 19:262.
19. Baumgartner JD, Vaney C, Perret C. An extreme form of the hyperdynamic syndrome in septic shock. *Intensive Care Med* 1984; 10:245–249.
20. Vieillard-Baron A, Schmitt JM, Beauchet A, *et al.* Early preload adaptation in septic shock? A transesophageal echocardiographic study. *Anesthesiology* 2001; 94:400–406.
21. Jardin F, Fourme T, Page B, *et al.* Persistent preload defect in severe sepsis despite fluid loading. *Chest* 1999; 116:1354–1359.
22. Poelaert J, Declercq C, Vogelaers D, *et al.* Left ventricular systolic and diastolic function in septic shock. *Intensive Care Med* 1997; 23:553–560.
23. Kakiyama Y, Ito T, Nakahara M, *et al.* Sepsis-induced myocardial dysfunction: pathophysiology and management. *J Intensive Care* 2016; 4:22. doi: 10.1186/s40560-016-0148-1.
24. Huang SJ, Nalos M, McLean AS. Is early ventricular dysfunction or dilation associated with lower mortality rate in adult severe sepsis and septic shock? A meta-analysis. *Crit Care* 2013; 17:R96.
25. Berrios RAS, O'Horo JC, Velagapudi V, Pulido JN. Correlation of left ventricular systolic dysfunction determined by low ejection fraction and 30-day mortality in patients with severe sepsis and septic shock: a systematic review and meta-analysis. *J Crit Care* 2014; 29:495–499.
26. Landesberg G, Gilon D, Meroz Y, *et al.* Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J* 2012; 33:895–903.
27. Mawri S, Alsafadi MY, Jain T, *et al.* Diastolic dysfunction in septic shock: insights from echocardiography. *Chest* 2016; 150:335A.
28. Kimchi A, Ellrodt AG, Berman DS, *et al.* Right ventricular performance in septic shock: a combined radionuclide and hemodynamic study. *J Am Coll Cardiol* 1984; 4:945–951.
29. Lanspa MJ, Cirulis MM, Wiley BM, *et al.* Right ventricular dysfunction in early sepsis and septic shock. *Chest* 2020; 159:1055–1063.
- A secondary analysis of a prospectively identified cohort of ICU patients admitted with severe sepsis or septic shock. RV dysfunction was frequently associated with LV dysfunction (91%). RV dysfunction in 48% of patients and threefold higher 28-day mortality in both univariate and multivariate analysis after adjustment for the presence of LV dysfunction. Mortality was lower in isolated LV dysfunction.
30. Kim J, Kim Y, Kim M, *et al.* Association between right ventricle dysfunction and poor outcome in patients with septic shock. *Heart* 2020; 106:1665–1671.
- A retrospective single-center study suggesting that RV failure is associated with higher 28-day mortality.
31. Vallabhajosyula S, Kumar M, Pandompam G, *et al.* Prognostic impact of isolated right ventricular dysfunction in sepsis and septic shock: an 8-year historical cohort study. *Ann Intensive Care* 2017; 7:94. doi: 10.1186/s13613-017-0319-9.
32. Harjola VP, Mebazaa A, Čelutkienė J, *et al.* Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. *Eur J Heart Fail* 2016; 18:226–241.
33. Lahm T, Douglas IS, Archer SL, *et al.* Assessment of right ventricular function in the research setting: knowledge gaps and pathways forward. An Official American Thoracic Society Research Statement. *Am J Respir Crit Care Med* 2018; 198:e15–e43.
34. Vieillard-Baron A, Prigent A, Repessé X, *et al.* Right ventricular failure in septic shock: characterization, incidence and impact on fluid responsiveness. *Critical Care* 2020; 24:630. doi: 10.1186/s13054-020-03345-z.

An ancillary study of the HEMOPRED study showing RV failure in 42% of patients with a negative effect on the fluid challenge response, despite significant PPV. TAPSE was not able to differentiate patients with or without RV failure.

35. Sanchez-Pinto LN, Luo Y, Churpek MM. Big data and data science in critical care. *Chest* 2018; 154:1239–1248.
36. Rhodes A, Evans LE, Alhazzani W, *et al.* Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2016; 43:304–377.
37. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. *Intensive Care Med* 2018; 44:925–928.
38. Gordon AC, Perkins GD, Singer M, *et al.* Levosimendan for the prevention of acute organ dysfunction in sepsis. *New Engl J Med* 2016; 375:1638–1648.
39. Geri G, Vignon P, Aubry A, *et al.* Cardiovascular clusters in septic shock combining clinical and echocardiographic parameters: a posthoc analysis. *Intensive Care Med* 2019; 45:657–667.
40. Husson F, Josse J, Pagès J. Principal component methods—hierarchical clustering—partitional clustering: why would be need to choose for visualizing data? Technical report 2010; 1–17.
41. Forte JC, Perner A, Van der Horst ICC. The use of clustering algorithms in critical care research to unravel patient heterogeneity. *Intensive Care Med* 2019; 45:1025–1028.
42. Liu R, Greenstein JL, Granite SJ, *et al.* Data-driven discovery of a novel sepsis preshock state predicts impending septic shock in the ICU. *Nature* 2019; 9:6145.
43. Knox DB, Lanspa MJ, Kuttler KG, *et al.* Phenotypic clusters within sepsis-associated multiple organ dysfunction syndrome. *Intensive Care Med* 2015; 41:814–822.
44. Seymour CW, Kennedy JN, Wang S, *et al.* Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. *JAMA* 2019; 321:2003–2017.